DATA EVALUATION RECORD

STUDY/ACTION TYPE: Rat teratology

CHEMICAL: Technical grade dinoseb

TEST MATERIAL: technical grade dinoseb; brown-yellowish resin; code DBS 071085; purity 96.1%; analyzed by HPLC for concentrations and homogeneity in vehicle (corn oil); reported as stable for at least 3 years when stored at -20 degrees centigrade

STUDY I.D.:

a. Embryotoxicity study with DINOSEB TECHNICAL GRADE (CODE: DBS 071085) in Wistar/HAN rat (Kfm: WIST, outbred, SPF quality)

b. Laboratory: RCC, Research and Consulting Company and RCC, Umweltchemie AG, CH 4452 Itinger/ Switzerland

c. Sponsor: DINOSEB TASK FORCE, c/o John Conner, Jr, Mc Kenna, Conner and Cuneo, 1575 Eye Street, N.W., Washington, D.C. 20005

d. Study #: Project # 045281

e. Date of Report: April 22, 1986

f. Study Director/Monitor: Dr. K.H. Leist

g. Caswell # 392DD, Accession #s 263765, 263766; EPA ID # 54299-Q

CONCLUSIONS:

Based on moderate body weight depression observed at the high dose, a maternal toxicity NOEL of 3 mg/kg/day is determined. Developmental toxicity is observed at the high dose level as evidenced by a slight depression in fetal weight and a relative increase in the reported incidence of absence of ossification for a number of skeletal sites as compared to control incidences, such as the phalangeal nuclei (right forelimb) of digit 1, digit 2 of distal phalange 2, and cervical vertebrae 1 or 2. There was also a comparative increase in the number of supernumerary ribs (left or right sides of rib 14). Based on these findings a developmental toxicity NOEL of 3 mg/kg/day is established. The developmental toxicity index (A/D) is 1.0 and Dinoseb is considered a "coeffective" developmental toxicant in rats, that is, developmental toxicity occurs in the fetuses at a dose level which also adversely affects the dams.

The study is designated as Core Supplementary data, with the possibility of upgrading to Core Minimum if individual litter data for skeletal variations are submitted and are found acceptable.

EXPERIMENTAL PROCEDURES:

Copies of the materials and methods section is attached (Attachment I). The following comments are noted for the study:

a. Animals had access to 8 hours of music/day.

b. Corrected body weight gain was calculated by the author using the formula:

Weight on day 21 - weight on day 6 - uterine weight (and expressed as percentage of day 6 body weight).
Instead of : Weight on day 21 - weight on day 0- uterine weight. (Note: the author's approach is acceptable if no differences in body weights among groups were noted on day 6 of gestation).

c. Food consumption was calculated using the formula:

$$\frac{\text{Grams of food consumed per period}}{\text{Days per period}} = \text{gm food/animal/day}$$

Four periods were used by the author for calculation: days 0-6, 6-11, 11-16 and 16-21 with food consumption data recorded on days 6, 11, 16 and 21. A true daily food consumption value would be:

Daily food offered - Food left, next day = Daily food consumption/animal

d. There is a lack of individual fetal variation data/litter for each dose group.

e. Long-term stability of the test material is stated but no evidence for this is given.

f. No individual clinical signs and symptoms or necropsy data were submitted, although it was stated in the report that no unusual findings were apparent.

g. The reviewer finds it unusual that no visceral findings were reported for 515 fetuses examined; this might suggest that some malformations/anomalies were overlooked. Examination of the historical control data report (pgs. 112-114) suggests that the reported incidence of visceral or skeletal variations are generally reasonable. For example, control data from teratology studies in Charles River CD rats (David C. Woo, MARTA Joint Study on Control Data of Teratological Studies in Charles River CD Rats; presented at refresher course during 1984 Teratology Society) shows an incidence of 22.5/10,000 (0.225%) fetuses for wavy ribs as opposed to 55/23566 (0.233%) in the present study; the incidence of hydrocephaly was 3.8/ 10,000 (0.038%) vs 3/23566 (0.0127%), respectively; the incidence of bipartite sternebrae was 1.1/10,000 (0.01%) vs 28/23566 (0.119%), respectively; dilatation of renal pelves 25.3/10,000 (0.253%) vs 48/23566 (0.204%)[both kidneys], respectively. However, it should be noted that no incidence of exencephaly, diaphragmatic hernia, hydronephrosis or general minor skeletal retardation was reported, although these anomalies/variations were observed in the MARTA study (0.02%, 0.041%, 0.567% and 0.093%, respectively).

Maternal Toxicity:

a. Mortality: No deaths were reported during the study for any female on test.

b. Clinical signs and symptoms: No signs or symptoms of dinoseb toxicity were reported.

c. Necropsy findings: No pathological findings were noted in any female of any group.

d. Body weights:

A summary of mean body weight gain data (gms) is presented below:

MATERNAL BODY WEIGHT GAINS[a]

| | Control | 1 mg/kg | 3 mg/kg | 10 mg/kg |
|---|---|---|---|---|
| Days 0-6 | 21 | 22 | 21 | 20 |
| Days 6-11 | 17 | 17 | 17 | 12 |
| Days 11-16 | 27 | 26 | 25 | 24 |
| [Sum of days 6-16 | 44 | 43 | 42 | 36] |
| Days 16-21 | 49 | 49 | 51 | 52 |
| Corrected body weight gain | | | | |
| -As presented in report[c] | 20 | 17(85)[b] | 16(80) | 13(65) |
| -As recalculated[d] | 41 | 38(93) | 36(88) | 33(80) |

[a] (Average dam weights) - (average body weight at 0, 6, 11, 16 days post-coitum) with weights totaled
[b] % control in parenthesis
[c] Body weight day 21 - weight on day 6 - uterine weight
[d] Average body weight at day 21 - average weight on day 0 - average uterine weight

Maternal mean body weight gain does not appear affected for any dose group except for a moderate reduction (20 to 30%) in the high dose group for days 6-11 when compared against the controls (17gms/control vs 12 gms/high dose) or when total body weight gains for the dosing period are compared (44 gms/ control vs 36 gms/high dose). Corrected body weight gains, which consider the uterine weight, using the author's method or calculated with day 0 control body weights, also suggest an moderate effect of dinoseb on the dams in the high dose group (65% of control or 80%, respectively) as evidenced by body weight depression.

e. Food consumption: The mean food consumption (g/animal/day) does not appear to be affected by dinoseb administration at any dose group during the time periods examined (0-6, 6-11, 11-16 and 16-21 days). However, expression of the data as absolute numbers(grams body weight/grams food consumed) rather than as the mean of food consumed per period/animal/day(as reported), may have more meaning due to body weight differences between the various dose groups.

Calculation of food efficiency during and after the dosing period yields the following data: (Food efficiency = average body weight increase/average amount of food consumed)

| Dose groups | Days 6-16(Dosing) | Days 16-21(Post-dosing) |
|---|---|---|
| Control | 0.114 | 0.349 |
| 1 mg/kg | 0.113 | 0.363 |
| 3 mg/kg | 0.111 | 0.370 |
| 10 mg/kg | 0.096 | 0.361 |

Apparently, the food efficiency ratio was slightly lower during the dosing period (days 6-15) for the high dose group as compared to the controls. However, comparable FEs were noted among the treated and control groups during the post-dosing period. This suggests a possible treatment-related effect at the high dose,i.e., decreased conversion of ingested food into body mass, and is consonant with observed effects on maternal body weights.

f. Summary of reproductive/fetal data

The reproductive data at necropsy are presented in a table below:

Reproductive Status at Necropsy[a]

| | Control | 1 mg/kg | 3 mg/kg | 10 mg/kg |
|---|---|---|---|---|
| # dams | 25 | 25 | 25 | 25 |
| # dams pregnant | 23 | 19 | 24 | 25 |
| Pregnancy index(%) | 92 | 76 | 96 | 100 |
| # dams aborted | 0 | 0 | 0 | 0 |
| # dams pregnant and dead | 0 | 0 | 0 | 0 |
| # litters examined | 23 | 19 | 24 | 25 |
| $\bar{x}$ corpora lutea (S.D.) | 12.4(2.0) | 12.8(1.9) | 14.0(1.9) | 13.4(1.4) |
| $\bar{x}$ Implantations (S.D.) | 11.6(3.2) | 11.9(2.7) | 12.7(2.8) | 12.3(2.2) |
| $\bar{x}$ Pre-implantation loss(%)/ mean # lost per dam | 6.7/0.8 | 7.0/0.9 | 9.0/1.3 | 7.8/1.0 |
| $\bar{x}$ Resorptions per dam | 0.7 | 0.5 | 1.0 | 0.9 |
| $\bar{x}$ Dead fetuses per dam | 0.0 | 0.0 | 0.0 | 0.0 |
| $\bar{x}$ Post-implantation loss | 0.7 | 0.5 | 1.0 | 0.9 |
| $\bar{x}$ Post-implantation loss(%) | 5.6 | 4.0 | 7.9 | 7.1 |
| $\bar{x}$ Live fetuses per dam(S.D.) | 10.9(3.2) | 11.5(2.5) | 11.7(3.0) | 11.4(2.6) |
| $\bar{x}$ Fetal weights (g)[S.D.] | 4.9[0.4] | 4.8[0.4] | 4.8[0.4] | 4.7[0.4]* |
| Sex ratio (% Males) | 51.4 | 52.8 | 48.4 | 53.1 |

[a] as reported in the study

* reported (p. 18) statistically significantly reduced from control value, although not indicated as such in summary table of reproduction data

No significant effect of dinoseb administration on any of the maternal reproductive parameters examined were observed, including mean number of pre-implantation loss, implantations, resorptions or post-implantation loss, number of fetuses per dam or dams aborted. The pregnancy index was relatively low (76%) as compared to the controls for the low dose level but this finding was inversely dose-related.

Fetal Toxicity

There was a slight, statistically significant fetal weight depression at the high dose level as compared to the control weights (4.9/control vs 4.7/high dose)(see summary reproductive table above).

No frank teratogenic effects were observed in the rat fetuses, in contrast to that observed in rabbit fetuses exposed orally to dinoseb (see memo of J. Rowe to R. Mountfort/J. Stone re: dinoseb review of June 18, 1986). However, there appears to be a relative increase at the high dose level as compared to the controls in the reported incidence of absence of ossification or supernumery ribs (Attachment II).

A few of the more obvious ossification findings are in the phalangeal nuclei (right fore limb): of digit 1 of distal phalange (12.6%/ control vs 30.3%/high), digit 2 distal phalange (8.7%/ control vs 22.1%/high), digit 5 proximal phalange (42.5%/control vs 64.1%/ high); phalangeal nuclei (left fore limb): digit 1 distal phalange (16.5%/control vs 31.7%/high), and digit 4 distal phalange (7.9%/control vs 17.2%/ high). Increased findings of absent ossification are also observed in the cervical vertebrae (vertebra 1= 7.1%/control vs 16.6%/high; vertebra 2= 17.35/control vs 35.2%/high). An increased incidence of supernumery ribs was observed in either the left or right sides (rib no. 14: left= 4.7%/control vs 16.6%/high; right= 3.9/control vs 11.7%/high).

DISCUSSION

Maternal toxicity from oral administration of dinoseb to the dams is minimal with no reports of mortality or clinical signs of toxicity, or gross pathology findings. There appears to be a moderate reduction in the mean body weight gain for days 6-15 in the high dose group as well as in the body weight gain corrected for the uterine weights. The food effeciency ratio also appears slightly lower at the 10 mg/kg/day dose level during the dosing period suggesting a treatment-related effect . Reproductive parameters are not signficantly affected for the dams. Thus, based on moderate body weight depression observed at the high dose, a maternal toxicity NOEL of 3 mg/kg/day is determined.

There is a slight but statistically significant depression in mean fetal body weights at the high dose. Other forms of developmental toxicity observed at the high dose level include a relative increase in the reported incidence of absence of ossification for a number of skeletal variations and supernumerary ribs. Based on these findings a developmental toxicity NOEL of 3 mg/kg/day is established. Since there is a small reduction in fetal weight, the increased incidence of absence of ossification as well as supernumerary ribs may relate to an inhibition of growth. Kavlock et al. (Terat.,Carcin., Mutagen.; 5:3-13; 1985) have reported in mice that the incidence of supernumerary ribs increased in response to nonspecific maternal toxicity. The developmental toxicity index (A/D) is 1.0 and Dinoseb is considered a "coeffective" developmental toxin in rats, that is, developmental toxicity occurs in the fetuses at a dose level which also adversely affects the dams.

This study is designated as Core Supplementary data, with the possibility of being upgraded to Core Minimum if individual litter data for skeletal variations are submitted.

Tox Chem No. 392DD-Dinoseb | File Last Updated 6/6/86 | Current Date 8/1/86

| GL Ref Study/Lab/Study #/Date | Material | EPA Accession/ MRID No. | Results: $LD_{50}$, $LC_{50}$, PIS, NOEL, LEL | TOX Category | CORE Grad Doc. No |
|---|---|---|---|---|---|
| 83-3 Rat teratology<br>Lab: Research and Consulting Company and RCC, Umweltchemie AG, CH 4452 Itinger/Switzerland<br>Study #: 045281<br>Date: April 22, 1986 | Technical; brown-yellowish resin; code DBS 071085; 96.1% purity | A 263765, 263766 | Levels tested: 0, 1, 3, 10 mg/kg/d (d 6-15 gestation)<br>Developmental toxicity NOEL= 3 mg/kg/d<br>effects:relative increase in reported incidence of absence of ossification for a number of skeletal sites (phalangeal nuclei, cervical vertebrae,etc.) and supernumerary ribs (left or right sides of rib 14) at high dose<br>Maternal systemic NOEL= 3 mg/kg/d<br>effects: moderate mean body weight depression<br>Developmental toxicity index (A/D) = 1.0; "coeffective" developmental toxicant | | Supplementary |

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| GL Ref Study/Lab/Study #/Date | Material | EPA Accession/ MRID No. | Results: $LD_{50}$, $LC_{50}$, PIS, NOEL, LEL | TOX Category | CORE Grad Doc. No |
|---|---|---|---|---|---|
| 83-3 Rat teratology Lab:Drug Safety,Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ Study#: XX85E-9999 (dose-ranging) Date: May 21, 1986 | Technical; brown-yellowish resin; code HOE 026015 OH ZD98 0004; 96.9% purity | A 263765, 263766 | Levels tested: 0,10,15,20,25,30 mg/kg/day(d 6-15 gestation) Results: dose-ranging study; maternal lethality at doses above 10 mg/kg/day; moderate or slight decreases in body wt. gain and food consumption at 10 mg/kg/day; minimal effects at 3 mg/kg/day for food consumption | | Supplementary |

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# 037316

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|---|---|
| **Chemical:** | **Dinoseb** |
| **PC Code:** | **037505** |
| **HED File Code** | **13000 Tox Reviews** |
| **Memo Date:** | **08/07/86** |
| **File ID:** | **TX005335** |
| **Accession Number:** | **412-03-0108** |

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